REMARKS

Claims 1, 3-10, 12-15, 20, 24-41 are currently pending in the application. Claim 1 has been amended to recite that:

- the pramipexole is in the form of pramipexole dihydrochloride monohydrate; support is found e.g., at [0050] and [0053] of US 2005/0175691
- the amount of pramipexole dihydrochloride monohydrate to about 0.1 to about 10 mg; support is found e.g., at [0053]
- the starch is in the amount of about 25% to 75% by weight; support is found at [0062]
- the hydrophilic polymer is in the amount of about 20% to 70% by weight; support is found e.g., at [0058]
- the pramipexole is dispersed in hydrophilic polymer and starch; support is found at e.g., [0055]
- Hydrophilic polymer functions to provide sustained release of the pramipexole; support is found at e.g., [0059]

New claims 28-34 recite preferred amounts of pramipexole dihydrochloride monohydrate; support is found, e.g., at [0053] and the examples. New claims 35 and 36 recite preferred amounts of starch; support is found, e.g., at [0062]. New claims 37-39 recite preferred amounts of hydrophilic polymer; support is found, e.g., at [0058]. New claim 40 relates to a "tablet"; support is found at [0052] and the examples. New claim 41 finds its basis at e.g., [0015] and claim 1 as filed.

In view of the amendments herein and the remarks below, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections and objections set forth in the November 12, 2009 Office Action.

Terminal Disclaimer

The Action indicates that the Terminal Disclaimer filed does not comply with 37 CFR 1.321(b) because the person who signed it is not recognized as an officer and not established to act on behalf of assignee. Applicants had filed a Statement under 37 C.F.R. 3.73(b) to remedy this, but the Action indicates that at the time the TD was filed it was defective, and filing of the statement under 37 C.F.R. 3.73(b) does not remedy this. In other words, the Examiner appears to

be saying that the Statement under 3.73(b) cannot be filed after the Terminal Disclaimer.

It is assumed that the Examiner is referring to the portion of 3.73(b) which states that: "For patent matters only: (1) Establishment of ownership by the assignee must be submitted prior to, or at the same time as, the paper requesting or taking action is submitted."

However, if the establishment of ownership is submitted after the paper requesting action (i.e., the terminal disclaimer), the disclaimer is effective at the time of the submission of the Establishment of ownership. There is no need to resubmit the terminal disclaimer. In particular, Examiner is respectfully referred to MPEP 324 which states:

> The establishment of ownership by the assignee must be submitted prior to, or at the same time as, the paper requesting or taking action is submitted. 37 CFR 3.73(c). If the submission establishing ownership is not present, the action sought to be taken will not be given effect. If the submission establishing ownership is submitted at a later date, that date will be the date of the request for action or the date of the assignee's action taken.

For this reason, it is submitted that there is no need for submission of a new terminal disclaimer.

Information Disclosure Statement

The Examiner's consideration of the Information Disclosure Statement submitted October 5, 2009 is thankfully noted.

Withdrawn Rejections

Withdrawal of the prior art rejection contained in the prior Office Action is noted with appreciation.

Claim Objection

Claim 21 stands objected to as in improper dependency because it recites that pramipexole is in the form of "one to a small plurality of dosage units", while claim 1 from which it depends recites that the composition is "in a single dosage unit". Claim 21 has been cancelled herein.

Rejections Under 35 USC § 112, second paragraph

Claims 1, 3-10, 12-21 and 23-25 stand rejected under 35 USC § 112, second paragraph, as indefinite for reciting "about" with respect to ranges recited in those claims. In particular, the Office Action indicates "no more than about", "greater than about", "at least about", "not greater than about", "about 0.1 to about 10", "about 0.2 to about 6", and "about 0.3 to about 5" are

vague, stating that "about" implies "that values other than the recited values are encompassed within the range". The Office Action states that it is unclear where the range begins and ends and what values are encompassed when the range includes the term "about". For the reasons that follow, withdrawal of this rejection is respectfully requested.

Applicants note that it is well settled that definiteness under 35 U.S.C. §112, second paragraph is analyzed "not in a vacuum, but always in light of the teachings of the prior art and in the particular application disclosure as it would be interpreted by one possessing the level of ordinary skill in the pertinent art". Energizer Holdings Inc. v. USITC, 435 F21 1366, 1370, 77 USPQ 1625, 1628 (Fed Cir 2006). The case law has indicated that the claims must be sufficiently definite to so that one skilled in the art can determine with a reasonable degree of certainty whether his or her conduct is within or outside the scope of the claim.

Nevertheless, use of the term "about" has been found to be appropriate. See, for example B.J. Services Co v. Halliburtan Energy Services Inc., 338 F3d 1368, 67 USPQ 2d 1692 (Fed Cir), cert denied, 2003 US App Lexis 22688 (2003), Merck & Co., Inc. v Teva Pharmaceuticals, USA, Inc. 395 F3d 1364 79 USPQ 2d 1641 (Fed Cir 2005). As employed in the specification, the term "about" is used in the ordinary meaning. It has been found that the term "about" in this context is not presumed indefinite.

It is noted that a primary objective of the present invention is the treatment of conditions (e.g., Parkinson's disease) by a once daily administration of a new sustained release pharmaceutical composition with pramipexole dichloride monohydrate as the active ingredient, which results in an all day delivery of this drug to the target organ. This result is achieved in that the active ingredient is dissolved from the composition over the range of about 24 hours in order to provide a substantially constant blood plasma level. Within this context, it is submitted that one of ordinary skill in this art would understand what is intended with respect to parameters such as hours as a measure for a period of time, or weight percentages/amounts of compounds in mg as a measure of the resulting dissolved or absorbed active ingredient. This would be understood in the claimed context of a composition administered once a day which provides pramipexole dichloride monohydrate that exhibits the recited bioavailability, i.e., substantially equivalent to an equal daily dose of immediate release formulation.

Furthermore, a review of the specification is submitted to demonstrate that the terms "no more than about", "greater than about", "at least about", "not greater than about" are not indefinite. These terms are used in the context of an "in vitro release profile "and an in vivo absorption profile". As described in the specification (and recited in the claims), the %

dissolution of pramipexole dihydrochloride in aqueous solution can be determined experimentally using the procedure disclosed. The specification provides the graph depicted in Figure 1. As gleaned from Figure 1, the amount of drug dissolved can be determined experimentally. A potential infringer can make the same determination as to whether the potentially infringing pharmaceutical composition has a dissolution profile wherein on average no more than about 20% of the pramipexole hydrochloride dissolves within 2 hours after placement thereof in a standard dissolution test, in accordance with the protocol described. Further, another an example of a graph from a human PK study showing the time course of mean plasma pramipexole concentration is depicted in Figure 2. (See also the experimentation described in Example 7 and the corresponding in-vivo absorption data set forth in Table 7.) The potential infringer can conduct similar testing to determine the mean in vivo absorption times of the product and determine whether the product infringes. Thus, it is respectfully submitted that terms such as "a time to reach mean of 20% absorption is greater than about 2 hours" and/or "the time to reach a mean of 40% absorption is greater than about 4 hours", as recited in Claim 1, or "the time to reach a mean of 40% absorption is at least about 5 hours", as recited in Claim 9 are not vague. Similarly, the phrases "a maximum plasma concentration of pramipexole that is at least about 6 hours..." "or at least about 8 hours" etc. (Claims 13-14), are submitted not to be vague as a potential infringer can conduct experiments as described in the instant application to determine the time it takes to reach maximum plasma concentration (Tmax).

Applicants' arguments are believed to be consistent with case law in this area. See W.L. Gore and Associates, Inc. v. Garlock, Inc., 721 F2d 1540 1557, 200 USPQ 303, 316, (Fed Cir 1983). For example, it has been held that the phrase "stretching in at a rate exceeding about 10% per second" was not vague, as infringement was clearly determinable through use of a stopwatch, i.e., by measurement. Similarly to Gore, infringement here can be determined by conducting the *in vitro* dissolution test and *in vivo* absorption test as described in the application.

For these reasons, the rejection on this bases under 35 U.S.C. § 112, second paragraph is submitted to be obviated, and withdrawal thereof is respectfully requested.

Claim 15 stands rejected under 35 U.S.C. § 112 on the basis that the term "a fluctuation ratio that is not substantially greater than that of an equal daily dose of an immediate release pramipexole dihydrochloride reference formulation administered three times a day" is vague. More specifically, the Office Action alleges that the "immediate release pramipexole dihydrochloride reference formulation" is unclear. As indicated above, definiteness is analyzed in view of the relevant application's disclosure. Throughout the instant specification, reference

is made to MIRAPEX® tablets. See paragraphs [0003] to [0005] where such specific reference is made (including reference to the relevant 2003 PDR pages), as well as at [0041] and in the Examples at Tables 8 and 9. From this context, it is submitted to be clear that the referenced immediate release pramipexole dihydrochloride formulation is the abovementioned MIRAPEX® immediate release tablet.

The Office Action also states that the term "not substantially greater" in the context of the fluctuation ratio is vague. The specification defines the fluctuation ratio as

$$FR=(C_{max}-C_{min})/C_{avg}$$

where C_{max}, C_{min} and C_{avg} are maximum, minimum and average plasma concentration respectively, of pramipexole. See paragraphs [0044]-[0045]. Attention is directed to Table 8 which compares the fluctuation ratio of MIRAPEX® immediate release tablets with three different exemplary sustained release tablets that provide sufficient insight into the term "not substantially greater". Based at least on these teachings in the specification, the meaning of this term is submitted to be clear.

Rejections under 35 U.S.C. §§102/103

Claims 1, 3-10, 12-21 and 23-25 stand rejected under 35 U.S.C. 102(a) and (e) as anticipated by, or under 35 U.S.C. §103 as obvious over Holman in view of Pospisilik '240 and Vandecruys et al. Applicants respectfully traverse this rejection.

Enclosed with this Amendment is the Declaration of John Heimlich, which addresses the references on which the rejection is based.

One basis for this rejection, though not solely relied on by the Examiner, is that Holman may describe a composition of pramipexole with other excipients, including pregelatinized starch and hydroxypropyl methylcellulose which inherently possesses the sustained release profile of the invention.

The invention of the present application relates to a sustained release pramipexole formulation having defined sustained release parameters and comprising, among other ingredients, a starch and a hydrophilic polymer. As amended, the current claims recite that the pramipexole is in the dihydrochloride monohydrate form, and that the formulation comprises about 20-70% of hydrophilic polymer and about 25 to 75% starch. The claims further state, as amended, that the pramipexole is dispersed in hydrophilic polymer and starch, and that said hydrophilic polymer functions to provide sustained release of the pramipexole.

As noted by Dr. Heimlich, Holman should not be properly read to disclose such a

composition. In particular, Holman does not appear to disclose a sustained release composition, but instead only an immediate release tablet.

For example, Holman discloses at column 11, line 42, a tablet containing as inactive ingredients lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxyl propylmethyl cellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide and polysorbate 80. This description reads to Dr. Heimlich, and he believes to anyone skilled in this art, as a film coated immediate release tablet. In particular, all ingredients listed in the first part of the formulation from "lactose" to "magnesium stearate" are typical components of the core of an immediate release tablet (lactose and starch are typical carriers, microcrystalline cellulose is a binding agent, sodium starch glycolate is a disintegrant and magnesium stearate is a lubricant). The remaining ingredients in the description, from "purified water" to "polysorbate 80", are typical film coating ingredients.

Accompanying Dr. Heimlich's declaration is a copy of a page from R.C. Rowe et al. (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London, UK (2003), which states that sodium starch glycolate is "widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations" (see p. 581, col. 1, next to last paragraph). Dr. Heimlich notes that the presence of sodium starch glycolate is not consistent with a pharmaceutical formulation having sustained release properties.

Holman also differs in that while it mentions hydroxypropyl methylcellulose, this is in connection with a film coating. In the present invention of an extended release composition, HPMC (hydrophilic polymer) in the composition provides, at least in part, for sustained release of pramipexole. The claims have been clarified in that they now recite that the pramipexole is dispersed in hydrophilic polymer; this differs substantially from Holman, which does not disclose pramipexole dispersed in HPMC (hydrophilic polymer). The claims have also been clarified to recite that hydrophilic polymer functions to provide sustained release, another significant difference from the Holman composition.

As Dr. Heimlich notes, for at least these reasons, he does not believe that the Holman pramipexole composition inherently possesses the sustained release characteristics of the instant invention. Nor are other parameters of the instant claims as amended met, as pointed out above.

Furthermore, when referring to pramipexole dihydrochloride monohydrate, Holman specifically refers to the "currently available" MIRAPEX® tablets. See column 8, lines 49-57; and column 11, lines 35-41. At the time when the Holman application was filed and later

issued, the only available MIRAPEX® tablets were the immediate release tablets. Furthermore, in the Holman specification at Column 8, Lines 49-57, reference is made to pramipexole dihydrochloride monohydrate available under the trademark MIRAPEX®, and further reference is made to the PDR, 53rd edition, 2497-2501, 1999. Thus, it is understood that reference to MIRAPEX® refers to the marketed immediate release pramipexole dihydrochloride monohydrate formulation described in the PDR.

Enclosed herewith are the referenced pages from the above-mentioned PDR. It is clear from the referenced pages that MIRAPEX® is an immediate release composition. As indicated therein MIRAPEX® is rapidly absorbed and "reach[es] peak concentrations in approximately 2 hours". See the section "Pharmacokinetics". Thus, MIRAPEX® does not, and can not, meet the extended release profile instantly claimed following administration.

Anticipation requires that the prior art reference teach and disclose every element of the claim, either implicitly or explicitly. Mehl/Biophile Int'l Corp v. Milgraum, 192 F3d, 1362, 1365, 59 USPQ 2d 1303, 1305 (Fed Cir 1999). The absence in the prior art of any element negates anticipation. Kalman v Kimberly Clark Corp., 713 F2d 760, 771-772, 218 USPQ 781, 789 (Fed Cir 1988). Holman does not teach, disclose or suggest a sustained release composition of pramipexole. It does not teach, disclose or suggest the release profile recited in the claims. Instead, the release profile indicated in the PDR for MIRAPEX® is consistent with an immediate release profile, not a sustained release composition.

Furthermore, a review of Holman reveals no teaching of the composition described therein as being a sustained release formulation. Thus, inasmuch as an element of the claims is not described or recited in Holman it cannot anticipate the claimed subject matter.

The Examiner has indicated that if Holman does not describe the invention, Pospisilik '240 (U.S. 2002/0103240) and Vandecruys (WO 00/59477) nevertheless provide the teachings that would be necessary to modify Holman to arrive at the invention with a reasonable expectation of success. Dr. Heimlich does not believe this to be the case.

Pospisilik '240 describes a process for resolving pramipexole into enantiomers. The only disclosure discernable by Dr. Heimlich in Pospisilik which is relevant to the present invention is the statement at ¶64 that controlled release formulations may be produced containing pramipexole and a "suitable" release controlling agent comprising water and/or a water-insoluble macromolecular substance such as an acrylate polymer or a modified cellulose.

This statement does not suggest to Dr. Heimlich, or it is submitted to others skilled in this art, that one would be able, with a reasonable expectation of success, to arrive at a sustained

release formulation of pramipexole comprised of about 20-70% of hydrophilic polymer and about 25 to 75% starch, wherein the pramipexole is dispersed in hydrophilic polymer which functions to provide sustained release, and wherein the composition when administered once daily exhibits bioavailability substantially equivalent to an equal daily dose of immediate release pramipexole administered three times a day. He does not see any indication of such a composition, or that it would be able to achieve such a result.

The Action appears to be relying on the Van de Cruuys reference to provide teachings missing from Holman and Pospsilik '240. The Van de Cruuys reference relates to controlled release compositions containing pregelatinized starch to prevent dose dumping, including those compositions wherein pregelatinized starch is combined with a hydrophilic polymer. The Action notes that the reference lists "anti-Parkinsonian drugs" as one type of drug that may be so formulated. The Action also points to a specific disclosure in Van de Cruuys of an example of a pharmaceutical formulation at Table 5 which displays release of the active ingredient at rates within the ranges recited in the current claims.

Dr. Heimlich does not read the Van de Cruuys reference to suggest making a sustained release formulation of pramipexole comprised of about 20-70% of hydrophilic polymer and about 25 to 75% starch, wherein the pramipexole is dispersed in hydrophilic polymer which functions to provide sustained release, wherein the composition when administered once daily exhibits bioavailability substantially equivalent to an equal daily dose of immediate release pramipexole administered three times a day. He also do not read this reference as providing any reasonable expectation of success that such a formulation would be successful.

The Van de Cruuys reference does not describe pramipexole (it only lists the anti-Parkinsonian agents bromocryptine mesylate, levodopa, and selegiline).

The Example pointed out by the Action, at Table 5, relates to Tablet 6, described at page 26. Tablet 6 contains the active agent 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridine-2(1H)-yl]ethyl]-2-methl-4H-pyrido[1,2-a]pyrimidin-4-one in a formulation which also contains cyclodextrin and lactose monohydrate. Cyclodextrin is normally added to a formulation to form a complex with poorly soluble active materials. Lactose monohydrate is normally added to aid in release of poorly soluble materials.

3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridine-2(1H)-yl]ethyl]-2-methl-4H-pyrido[1,2-a]pyrimidin-4-one is chemically distinct from pramipexole. Based on the use of appreciable quantities of both cyclodextrin and lactose monohydrate in the Van de Cruuys reference, Dr. Heimlich understands the formulation of Tablet 6 to relate to an extended release composition of

a poorly soluble active.

He does do not understand this disclosure to provide any indication of whether such a formulation, or any one which is similar, would or could provide the same sustained release properties for pramipexole. Pramipexole is highly soluble (about 20 mg/ml at 20-25°C). Such drugs can be difficult to formulate in sustained release dosage forms. The formulation of Tablet 6 provides little or nothing that could predict whether the instantly claimed formulation would exhibit the claimed properties.

Nor does he see any other disclosure in the Van de Cruuys reference which remedies such deficient teachings.

Thus for reasons described in Dr. Heimlich's declaration, Van de Cruuys does not provide the teachings missing from Holman and Pospisilik to arrive at the present invention.

The current amendments further distinguish Van de Cruuys (alone or in combination) from the current claims.

In particular, the Vandecruys reference discloses that pregelatinized starch may be present in a range from about 0.1 to less than 80% w/w [page 11, line 15] and the hydrophilic polymer may be present in a range from about 0.1 to about 80% w/w [page 12, line33]. However, the Vandecruys disclosure focuses on pharmaceutical formulations wherein the amount of pregelatinized starch is about 5%:

> *The weight percentage of pregelatinized starch in the hydrophilic controlled release formulation of the present invention preferably ranges from about 0.01 % to less than 80% (w/w), more preferably from about 0.01 % to about 15%, even more preferably from about 0.01 % to about 5%, and most preferred is about 5%.*

All the specific tablet examples made and tested in Vandecruys have amounts of starch in the very narrow range of 3% to 5% by weight. See Tablets 1 to 6 at pages 24-26.

As noted, the Examiner relies upon the data in Table 5 relating to Tablet 6 (to which Table 5 refers). As described at the top of page 26, Tablet 6 has only about 3% by weight of starch. This is the lowest amount of starch of all the tablets described and tested in the reference. Furthermore, a review of the release data provided for the other tablets in Vandecruys (all of which have approximately 5% by weight of starch) indicates that the tablets of Vandecruys having higher amounts of starch show significantly faster release profiles than that of Tablet 6. See data of Table 1 for Tablets 1 and 2; and the data of Table 2 for Tablets 3 and 4. (Table 3 used tablets containing no starch; and Table 4 is directed to a mixture of active and a cyclodextrin, not starch-containing tablets).

Thus, the data in Vandecruys appear to indicate that even using a slightly higher amount of starch (from 3% to 5% by weight) would result in a faster in-vitro release profile for the active, outside the sustained release parameters instantly claimed.

By contrast, Applicants have determined that the instantly claimed extended release profile for pramipexole can be achieved even with relatively higher amounts of starch; this appears to be in contradiction to the teachings of Vandecruys.

The presently amended claims relate to an amount of starch that is higher, namely within a range from about 25% to about 75 % w/w, with a preference towards ranges of about 40% to 70% (new Claim 35) and 45% to 65% (new Claim 36).

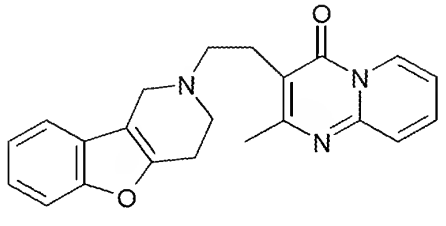
Applicants respectfully submit that Vandecruys does not suggest that the sustained release profile for pramipexole as instantly claimed can be achieved using such high amounts of starch.

New dependent claims 38 and 39 recite amounts of hydrophilic polymer in ranges from about 35% to about 60% by weight, and from about 35% to about 50% by weight, respectively.

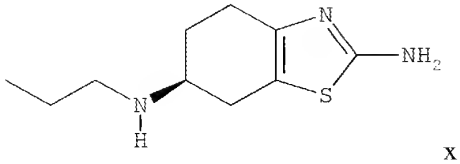
However, the specific example of Vandecruys relied upon by the Examiner as suggesting the instantly claimed release profile, i.e., Tablet 6, has one of the lowest amounts of hydrophilic polymer at about 32.4% by weight.

Applicants submit that Vandecruys does not suggest that the recited sustained release profile for pramipexole can be achieved using amounts of hydrophilic polymer recited in claims 38 and 39.

In addition, as alluded to by Dr. Heimlich, Table 5 describes a release profile of a completely different drug from pramipexole, namely 3-[2-[3,4-dihydrobenzofuro [3,2-c] pyridin-2(1H)-yl]-ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. This compound has the following structure:



Pramipexole dihydrochloride monohydrate has the following structure:



x 2 HCl x H_2O

The characteristics of the presently claimed composition can not, it is submitted, be properly predicted based upon a composition having such a structurally distinct active ingredient. (As noted by Dr. Heimlich, the actives appear to also have very different properties.)

Finally, none of the references taken alone or in combination suggest solving any problem associated with the dihydrochloride salt of pramipexole. It is only with the guidance provided by the present application that this problem is solved.

For these reasons, withdrawal is respectfully requested of the rejection of Claims 1, 3-10, 12-21 and 23-25 under 35 U.S.C. 102(a) and (e) as anticipated by, or under 35 U.S.C. §103 as obvious over, Holman in view of Pospisilik '240 and Vandecruys et al..

Rejections Under 35 USC § 103(a)

Claims 1 and 3-10, 12-21 and 23-25 stand rejected as obvious under 35 U.S.C. §103(a) over Pospisilik '240 in view of Vandecruys.

Applicants have extensively addressed the differences between the cited references and the presently amended claims in the rejection above. It is respectfully submitted that in view of these differences and the lack of suggestion of the claims, as described above, this rejection should be withdrawn.

Claims 1 and 3-18, 20 and 21 stand rejected as obvious under 35 U.S.C. §103(a) over Pospisilik '119 in view of Vandecruys.

Pospisilik '119 has substantially the same relevant disclosure as does Pospisilik '240. In view of the arguments above, withdrawal of this rejection is respectfully requested.

Rejection For Double Patenting

Claims 3-10, 12-21 and 23-25 stand provisionally rejected for obviousness-type double patenting over Claims 1-23 of co-pending Application Serial No. 10/626,166 ("the '166 Application"). Applicants have discussed the Examiner's objection to the filed Terminal Disclaimer above. Withdrawal of the double patenting rejection is requested.

Withdrawn Methods Claims 26-27

In the event composition claim 1 is found allowable, Applicants respectfully request rejoinder of the dependent method claims 26-27 under USPTO's Rejoinder Practice as outlined in MPEP § 821.04.

Conclusion

In view of the remarks above, Applicants respectfully submit that the pending claims are allowable, and request issuance of a notice to that effect. If a telephone interview is deemed to helpful, the Examiner is invited to contact applicants' undersigned attorney.

Respectfully submitted,

Dated: May 12, 2010

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Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Sodium Starch Glycolate

1 Nonproprietary Names

BP: Sodium starch glycollate
PhEur: Carboxymethylamylum natricum
USPNF: Sodium starch glycolate

2 Synonyms

Carboxymethyl starch, sodium salt; *Explotab*; *Primojel*; *Vivastar P*.

3 Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

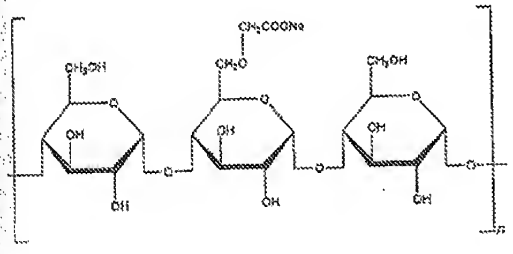
4 Empirical Formula Molecular Weight

The USPNF 20 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. The molecular weight is typically 5×10^5–1×10^6.

The PhEur 2002 describes three types of material; Type A, equivalent to the USPNF 20 material, containing 2.8–4.2% of sodium; Type B containing 2.0–3.4% of sodium; and Type C containing 2.8–5.0% of sodium.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule[1–6] and tablet formulations.[7–10] It is commonly used in tablets prepared by either direct-compression[11–13] or wet-granulation processes.[14–16] The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.[17–20]

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.[13,14]

Sodium starch glycolate has also been investigated for use as a suspending vehicle.[21,22]

8 Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30–100 µm in diameter, with some less-spherical granules ranging from 10–35 µm in diameter.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium starch glycolate.

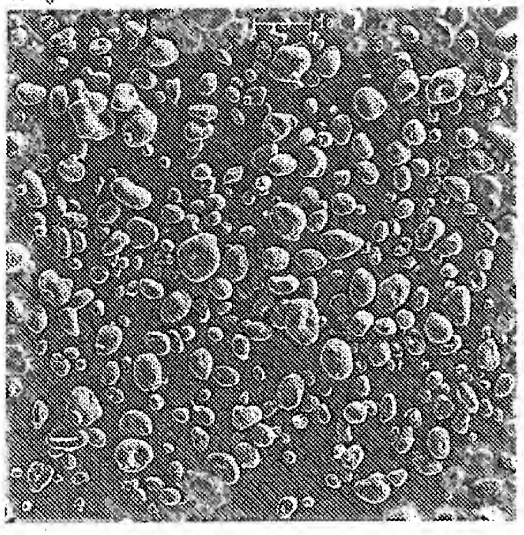
Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Appearance of solution	+	—
pH	+	3.0–5.0 or 5.5–7.5
Type A	5.5–7.5	—
Type B	3.0–5.9	—
Heavy metals	⩽20 ppm	⩽0.002%
Iron	⩽20 ppm	⩽0.002%
loss on drying	+	+
Type A	⩽10.0%	⩽10.0%
Type B	⩽10.0%	⩽10.0%
Type C	⩽7.0%	—
Microbial limits	+	+
Sodium chloride	+	+
Type A	⩽7.0%	⩽7.0%
Type B	⩽7.0%	⩽7.0%
Type C	⩽1.0%	—
Sodium glycolate	+	—
Assay (of Na)	+	—
Type A	2.8–4.2%	—
Type B	2.0–3.4%	—
Type C	2.8–5.0%	—

10 Typical Properties

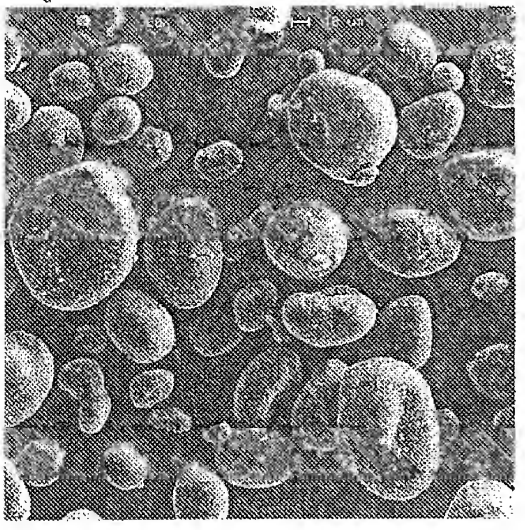
Acidity/alkalinity: pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3% w/v aqueous dispersion. *See* Section 18.
Ash: ⩽15%
Density (bulk): 0.756 g/cm^3
Density (tapped): 0.945 g/cm^3
Density (true): 1.443 g/cm^3
Melting point: does not melt, but chars at approximately 200°C.
Particle size distribution: 100% of particles less than 104 µm in size. Average particle size is 42 µm for *Explotab*.
Solubility: sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.
Specific surface area: 0.24 m^2/g
Swelling capacity: in water, sodium starch glycolate swells to up to 300 times its volume.

Viscosity (dynamic): ≤200 mPa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

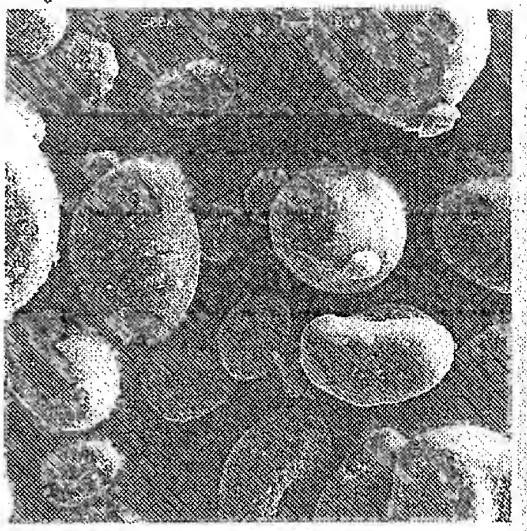
SEM 1
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 100×
Voltage: 10kV



SEM 2
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 300×
Voltage: 10kV



SEM 3
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 500×
Voltage: 10kV



11 Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties.[23–25] Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 4 years if it is stored at moderate temperatures and humidity.

12 Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.[26]

13 Method of Manufacture

Sodium starch glycolate is a substituted and crosslinked derivative of potato starch.

Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline medium followed by neutralization with citric acid or some other acid. Crosslinking may be achieved either by physical methods or chemically by using reagents such as phosphorus oxytrichloride or sodium trimetaphosphate.[27]

14 Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Pregelatinized starch; starch.

18 Comments

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage and extent of carboxymethylation.

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